

Letter

Deep inhalation bronchoprotection

When methacholine is inhaled with total lung capacity inhalations, which is the recommended inhalation pattern for the 5-breath dosimeter method,¹ as many as a quarter of asthmatic patients can have a false-negative test result.² It has been suggested to us that high forced expiratory volume in 1 second (FEV₁) could explain negative (dosimeter) methacholine test results in patients with asthma. We therefore decided to perform additional analyses on previously published data in 55 asthmatic patients comparing the 2 American Thoracic Society (ATS) methacholine methods.²

Bronchoprotection can be defined as the tendency of a drug or a maneuver to inhibit bronchoconstriction. In these 55 patients, the bronchoprotective effect of the 5 deep inhalations was expressed as the doubling concentration difference between the 2 methods. This was calculated by the following formula³: (log dosimeter PC₂₀ – log tidal breathing PC₂₀)/0.3 (where 0.3 is log 2 and PC₂₀ is provocation concentration that caused a decrease in FEV₁ of 20%).

We looked for linear regression correlation with baseline FEV₁ (the FEV₁ before the first of the 2 challenges) defined as FEV₁ percent predicted, FEV₁ absolute (liters), and FEV₁:forced vital capacity (FVC) ratio. We also sought correlation with (log) baseline tidal breathing PC₂₀ and (log) dosimeter PC₂₀.

For all regressions regarding lung function, there was a nonsignificant correlation for higher FEV₁ being associated with greater bronchoprotection (protection vs FEV₁ [percent predicted], $P = .16$; protection vs FEV₁ [liters], $P = .24$; and protection vs FEV₁/FVC ratio, $P = .11$). We demonstrated a significant positive correlation between baseline tidal breathing PC₂₀ and bronchoprotection (Fig 1, $r = 0.3$, $P = .03$). This finding demonstrates that the higher the baseline tidal breathing PC₂₀ the greater the bronchoprotective effect of the deep inhalations. Fourteen of the 55 patients (25%) had negative dosimeter challenge results as previously published.² In addition, the (expected) positive correlation was seen between the dosimeter PC₂₀ and bronchoprotection ($r = 0.81$, $P < .001$).

These results indicate that baseline FEV₁ is at most a minor determinate of the important bronchoprotective effect of the 5 deep inhalations required to perform the dosimeter methacholine challenge as per guidelines.¹ It is possible, in fact likely, that a larger study might have shown statistical significance, but this would be of limited clinical significance. The positive correlation with tidal breathing methacholine response, as previously shown by dichotomizing this population,² indicates that the deep inhalation bronchoprotection is more likely to occur in those with, as defined by the ATS,¹ mild (PC₂₀ of 1–4 mg/mL) to borderline (PC₂₀ of 4–16 mg/mL) airway hyperresponsiveness. The marked correlation with

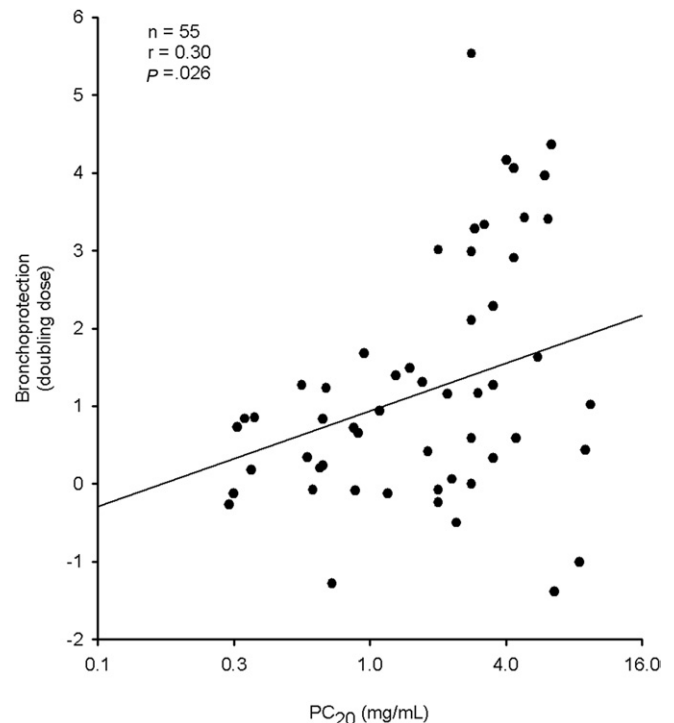


Fig. 1. Deep inhalation bronchoprotection vs baseline (tidal breathing) methacholine provocation concentration that caused a decrease in forced expiratory volume in 1 second of 20% (PC₂₀). Bronchoprotection is defined as the doubling dose difference in PC₂₀ between the 2 methods (dosimeter minus tidal breathing).

the dosimeter PC₂₀ is to be expected because the magnitude of the bronchoprotection is primarily determined by the magnitude of the dosimeter PC₂₀. Other features, such as rhinitis⁷ and obesity,⁸ have been shown to play a role in the effect of deep inhalations in the airways of individuals without asthma. A larger study in asthmatic patients would be required to investigate these and other potential factors in asthmatic patients.

We believe the importance of this bronchoprotective effect is often overlooked. Our data² demonstrate that a quarter of asthmatic patients with a positive tidal breathing methacholine test result have negative dosimeter test results. This number approaches 50% of patients when addressing those with mild to borderline airway hyperresponsiveness (ie, PC₂₀ of 1–16 mg/mL). This is the range most positive diagnostic methacholine challenge results would be expected to occur. The major value of methacholine challenge is the high diagnostic sensitivity and high negative predictive value,⁴ providing that symptoms are clinically current⁵ (ie, within the past day or two). We would also like to add the addi-

Disclosures: Authors have nothing to disclose.

tional caveat that the methacholine should be inhaled by submaximal inhalations to preserve the diagnostic sensitivity. The dosimeter method can be adequately and easily performed using submaximal inhalations.⁶

In summary, the important bronchoprotective effect of inhaling methacholine by total lung capacity inhalations does not depend on baseline FEV₁ but rather depends on baseline (tidal breathing) PC₂₀. We recommend that diagnostic methacholine challenges, performed by either method,¹ be performed without deep total lung capacity inhalations.

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References

- [1] Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999. *Am J Respir Crit Care Med.* 2000;161:309–329.
- [2] Cockcroft DW, Davis BE. The bronchoprotective effect of inhaling methacholine by using total lung capacity inspirations has a marked influence on the interpretation of the test results. *J Allergy Clin Immunol.* 2006;117:1244–1248.
- [3] O'Connor BH, Aikman SL, Barnes PJ. Tolerance to the nonbronchodilator effects of inhaled β_2 agonists in asthma. *N Engl J Med.* 1992;327:1204–1208.
- [4] Cockcroft DW, Murdock KY, Berscheid BA, Gore BP. Sensitivity and specificity of histamine PC₂₀ in a random selection of young college students. *J Allergy Clin Immunol.* 1992;89:23–30.
- [5] Cockcroft DW, Hargreave FE. Airway hyperresponsiveness: relevance of random population data to clinical usefulness. *Am Rev Respir Dis.* 1990;142:497–500.
- [6] Todd DC, Davis BE, Hurst TS, Cockcroft DW. Dosimeter methacholine challenge: comparison of maximal versus submaximal inhalations. *J Allergy Clin Immunol.* 2004;114:517–519.
- [7] Crimi E, Saporiti R, Bartolini S, et al. Airway responsiveness to methacholine and deep inhalations in subjects with rhinitis without asthma. *J Allergy Clin Immunol.* 2008;121:403–407.
- [8] Skloot G, Schechter C, Desai A, Togias A. Impaired response to deep inspiration in obesity. *J Appl Physiol.* 2011;111:726–734.